

## Regulatory Issues of Tumor Markers: FDA/CLIA/etc

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Robert L. Becker Jr., M.D., Ph.D.  
Office of In Vitro Diagnostic Device Evaluation and Safety  
FDA/CDRH

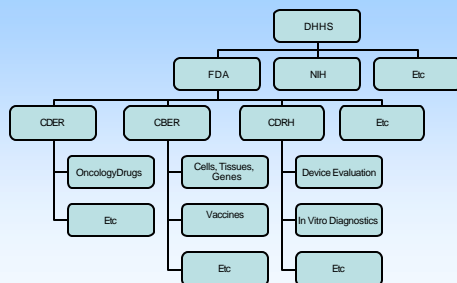


### Outline

- Discuss Devices structure and difference between Devices and Therapeutic Branches;
- Discuss meaning of FDA approval or clearance, with emphasis on new vs. equivalent submissions;
- Discuss laboratory developed tests and current status of need for FDA approval or not to market test.



### Organization (Abstracted)



### Medical Device Amendments of 1976

- General Controls
  - Adulteration and Misbranding
  - Registration and Listing
  - Pre-market Notification
  - Records and Reports
  - Good Manufacturing Practices
  - Other



### FDA Device Regulation

- Risk based (three classes)
  - General controls
  - Special controls (e.g., 510(k))
  - Pre-market approval
- Technology a factor, but not determinative
- Intended use and indications for use



### Risk-Based Classification of IVDs

- Class III: most complex, high risk
  - e.g. cancer diagnosis or screening
    - Premarket Application [PMA]
    - Safety, effectiveness
- Class II: more complex, moderate risk
  - e.g. prognosis, monitoring in already diagnosed cancer patients
    - Premarket Notification [510(k)]
    - Special controls
- Class I: common, low risk devices
  - Most exempt from premarket submission
  - General controls

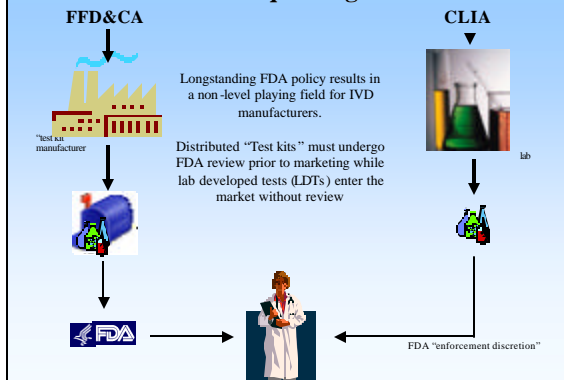
## Intended Use Determines Type of Submission

- A CFTR genotyping assay with the indication
  - For carrier screening → **510(k)**
  - For fetal screening → **PMA**
- One multiplex instrument system with 2 devices
  - Device detecting BCR-ABL for CML diagnosis → **PMA**
  - Device detecting BCR-ABL for monitoring → **510(k)**

## Some IVD Terminology

Class	Pre-market Submission	Success Metric	Action
3	PMA	Safety and Effectiveness	Approval
2	510(k)	Substantial Equivalence	Clearance
1	None (if exempt)		
2 (De Novo)	510(k)	Safety and Effectiveness	Clearance

## IVDs – Unequal Regulation



## LDTs – not trouble free

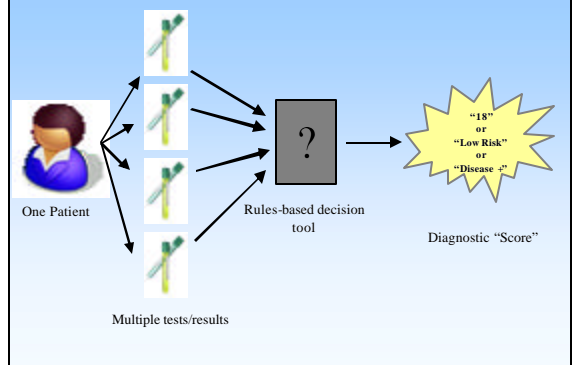
- Different regulatory threshold than FDA reviewed tests– non-parity
  - No premarket review
  - No independent research phase
  - No requirement for clinical validity
- Varying quality in test development and validation

## IVDMIA's

A growing category of new tests for clinical diagnosis are:

**In Vitro Diagnostic Multivariate Index Assays (IVDMIA's)**

## IVDMIA's





## IVDMIA Guidance Background

FDA published a draft guidance on IVDMIAs that defines a narrow niche of devices. The guidance states that these devices are subject to FDA regulation rather than enforcement discretion even when offered as laboratory developed tests.

FDA Concerns regarding lab developed IVDMIAs:

- No independent review of data sets or clinical claims – is it clinically valid?
- Degree of scientific rigor varies greatly among IVDMIA developers
- Some lab developed IVDMIAs offered for clinical use while still in a “research phase”



## IVDMIA Guidance Background

- Original draft guidance published September 7, 2006
- Public Meeting held February 8, 2007
- Revised draft issued July 26, 2007
- FDA received more than 50 comments  
Submitted primarily by IVDMIA developers, commercial laboratory groups, rare disease research advocates, consumer advocates, pharmaceutical companies, IVD manufacturers, 3<sup>rd</sup> party payers, cancer prevention groups, physicians, private citizens



## IVDMIA Guidance

### Exceptions:

- FDA will continue enforcement discretion for laboratory-developed IVDMIAs intended for rare disease testing
- Until FDA issues guidance on how labs may best meet FDA quality system requirements, FDA intends to exercise enforcement discretion with regard to post-market enforcement of QS requirements for such laboratories

(For PMA applications, FDA will work with the applicant to determine the least burdensome approach to developing QS compliant systems)



## IVDMIA Guidance

To provide sufficient time for IVDMIA manufacturers to come into compliance, FDA has proposed an initial transition period for currently marketed, laboratory-developed IVDMIAs.

This phased-in, 18 month transition period allows:

- 12 months for submission of a 510(k) or PMA
- 6 months additional enforcement discretion during FDA review of submission

Currently, FDA is reviewing comments received on the draft guidance



## Impact of FDA Regulation

- Independent assessment of data and labeling
- Adverse event reporting and Recalls
- Informed by evaluation standards; grounded in “least burdensome” mandate
- If focused – good science is good science

Note: If the test is already being used (or going to be used) on patients, shouldn’t data exist to show it is safe and effective?



## State of Affairs

- Industry seeking regulatory parity between IVDs and LDTs – including genetic tests
- Consumer advocates seeking more comprehensive regulatory assurance of LDTs and genetic tests, and more assurance of clinical validity and clinical utility
- Commercial Laboratories seeking predictability, some favor status quo or CMS (CLIA) regulation over FDA (FFD&CA) regulation



## State of Affairs (Cont'd)

- Congress concerned with issues
  - Kennedy, Obama bills
  - GAO DTC testing report
- Citizens' Petitions
  - Washington Legal Foundation
  - Genentech



## State of Affairs (Cont'd)

### Secretary Leavitt Priority: Personalized Medicine

SACGHS Oversight Report includes recommendations to:

- Require more proficiency testing for genetic tests
- Establish a mandatory registry for genetic tests
- Have FDA address clinical validity of all laboratory tests
- Increase research efforts to generate clinical utility information for genetic tests



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## Device Advice

- See the Center for Devices and Radiological Health website at <http://www.fda.gov/cdrh>, and especially its "Device Advice" link at <http://www.fda.gov/cdrh/devadvice>, for useful information about the regulation and review of medical devices, including in vitro diagnostic devices.
- See Office of Combination Products website at <http://www.fda.gov/OC/combination/>



## Additional Guidance Documents

- Drug-Diagnostic Co-Development Concept Paper
  - <http://www.fda.gov/Cder/genomics/pharmacoconceptfn.pdf>
- Guidance for Industry and FDA Staff Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions
  - <http://www.fda.gov/cdrh/oivd/guidance/1590.pdf>
- Draft Guidance for Industry, Clinical Laboratories, and FDA Staff - In Vitro Diagnostic Multivariate Index Assays
  - <http://www.fda.gov/cdrh/oivd/guidance/1610.pdf>



## Pre-IDE

- Not an IDE (just a misnomer)
- It is a protocol review and regulatory guidance
- No charge to the sponsor
- Non-binding on either party
- Recommended for novel devices / uses
- <http://www.fda.gov/cdrh/oivd/presentations/042203-Altaie.html>



## Questions?

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robertl.becker@fda.hhs.gov  
240-276-0843